

Claims 17-21 have been rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. Claim 17 has been amended to obviate many of the issues relating the indefiniteness of language in the claim. Claims 18-21 have been deleted. Applicants submit that Claim 17 is now in compliance with 35 USC §112, second paragraph.

Claims 17-20 have been rejected under 35 USC §102(b) as being anticipated by the Fujimaki et al. reference, US Patent No. 4,016,147. The Examiner believes that the Fujimaki et al. reference discloses a bioactive composition produced by hydrolysis of a protein source and at a controlled acidic pH with pepsin from fish as the hydrolytic enzyme. Applicant believes that it is well-known to have a mixture of peptides which have aromatic acids in the N-terminal portion, for example, phenylalanine and tyrosine.

Claim 17 has been amended and the amended claim is not anticipated by the Fujimaki et al. reference. The reference is directed towards the preparation of low phenylalanine plasteins, and certain synthetic protein-like substances. Indeed, the teaching of the disclosure is towards a novel synthetic protein-like substance. In addition, hydrolyzates are obtained that are free from aromatic amino acids, which are required in the presently claimed invention. Further, enzymes from the stomach of Atlantic Cod fish are not shown to be hydrolytic enzymes in the process of the Fujimaki et al. reference. The differences in the composition of the claimed invention versus the Fujimaki et al. reference are critical to produce the bioactive peptide. The invention as

claimed is distinct from the Fujimaki et al. reference, and therefore the Fujimaki et al. reference does not anticipate the claim of the present invention.

Claims 17-20 have been rejected under 35 USC §102(b) as being anticipated by the Yamashita et al. reference. The Examiner indicates that the Yamashita et al. reference discloses a bioactive composition produced by hydrolysis of a protein source at a controlled acidic pH with pepsin from fish as a hydrolytic enzyme. The Yamashita et al. reference does not anticipate the present invention as claimed. Claim 17 of the present invention requires pepsin obtained from the stomach of Atlantic cod. The Yamashita et al. reference relates to the preparation of a peptide type low phenylalanine, high tyrosine food for curing phenylketonuria. A fish protein and a soybean protein isolate are used as starting materials. The peptic hydrozylate is further hydrolyzed with pronase under unconventional pH conditions to liberate amino acids that are removed by absorption activity. The resulting amino acid free fractions are mixed with ethyl esters of L-tyrosine and L-tryptophan and incubated with papain under certain conditions which are divergent from conditions needed to prepare the presently claim invention. Clearly, the Yamashita et al. reference does not anticipate claim 17 of the present invention.

Claims 17-20 have been rejected under 35 USC §103(a) as being unpatentable over the Fujimaki et al. reference, the Yamashita et al. reference, and the Gildberg et al. reference. The Examiner indicates that the Gildberg et al. reference teaches the isolation of peptide fractions from a fish protein hydrozylate from the stomach of Atlantic

cod in which the isolated or separated acid peptide fractions were used *in vitro* stimulatory experiments with head kidney leukocytes from Atlantic salmon. The Examiner believes that the Gildberg et al. reference teaches the use of the proteolytic enzyme derived from the stomach of Atlantic cod in hydrolyzing fish protein at a controlled pH and a process for the production of bioactive peptide compositions having amino acids in the N-terminal position.

The Gildberg et al. reference does not describe any process or process condition for making the claimed bioactive peptide composition. The reference merely refers to the fact that peptides present in empty Atlantic cod stomachs which have been left to undergo a self-digestion or autolysis under conditions which are not described or specified in the reference.

In the "Materials and Method" chapter of the reference at page 89, Gildberg et al. did not refer to any process conditions, that is temperature, type of acid, pH or incubation time for making the bioactive peptides that they studied. In trying to discover similarities, the Examiner may be referring to page 10 of the reference, referring to conditions 10°C, pH 2-3 using hydrochloric acid, Gildberg et al. used in performing the ion exchanged separation of the peptides. This process has nothing to do with the process of making such peptides.

It is basic biochemistry that proteins are degraded in the presence of proteolytic enzymes (hereunder pepsins) to peptides (with a number of amino acids ranging from


2-100) and free amino acids. Such a proteolytic process may exist under all possible conditions within the parameters of biological activity (pH 1-12, temperature 0-90°C, salt 0-23%, etc.), but never by one and the same proteolytic enzyme. The great number of proteolytic enzymes in nature attack proteins in different ways and under widely different conditions with the parameters of biological activity (pH 1-12, temperature 0-90°C, salt 0-23%, etc.). The resulting product mix, despite always being a mixture of peptides and amino acids, will accordingly differ with process conditions, protein substrate and enzyme activity, and time of enzymatic action. Sometimes bioactive (or immune stimulating) peptides may be formed, under other conditions, merely bioavailable amino acids, sometimes peptides which induce vomiting, sometimes peptides which enhance appetite, and so on. Moreover, a proteolytic enzyme may cause notable changes in the molecular/3-dimensional structure of a protein without degrading it to peptides.

Clearly, there is no indication that a secondary reference, the Gildberg et al. reference, can be added to the teachings of the Fujimaki et al. reference and the Yamashita et al. reference to correct the improper combination of those teachings. Therefore, the combination of references do not teach or suggest the present invention. Each of the references taken alone or in combination do not teach the subject matter of Claim 17.

It is respectfully submitted that the amended claim meets the requirements of 35 U.S.C. 112, 102 and 103. An early Notice of Allowance of the above-identified application is respectfully requested.

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Respectfully submitted,



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APPLICANT: Jan Raa et al.

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TITLE: Bioactive Peptides, Uses Thereof, and Process for the
Production of Same

The Assistant Commissioner for Patents
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) Group Art Unit: 1653
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) Examiner: A. Mohamed
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MARKED VERSION OF AMENDED CLAIM 17

17. A bioactive peptide composition consisting of a mixture of peptides having an aromatic amino acid in the N-terminal position, **selected from the group consisting of tyrosine, phenylalanine and arginine**, produced by enzymatic hydrolysis of a protein source **preferably from fish** at a pH in the range of 1-6 with pepsin **[derived]** **obtained from fish, preferably from the stomach of Atlantic cod** as the hydrolytic enzyme, **said bioactive peptide composition consisting of less than 100 amino acid units and having a molecular weight below 10,000 kd.**